## REMARKS/ARGUMENTS

Claims 124, 129-131, 135-150 were pending in this application. The rejections to the presently pending claims are respectfully traversed.

### Claim Rejections – 35 U.S.C. §101 and §112, First Paragraph

Claims 124, 129-131, 135-150 stand rejected under 35 U.S.C. §101 for lack of utility.

Claims 124, 129-131, 135-150 stand further rejected under 35 U.S.C. §112, first paragraph, allegedly since "the claimed invention was not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention."

The Examiner asserts that the arguments concerning gene amplification are not persuasive in overcoming the rejections because "the data (for PRO1182 DNA) shows an indeterminate increase in chromosome number in 3 cancerous lung tumor tissues out of 12 lung tumor tissues tested. However, there is no evidence regarding whether or not PRO1182 mRNA or polypeptide levels are reliably increased or decreased in cancer." (Page 4 of the instant Office Action). The Examiner maintains that "there is often a lack of correlation between gene amplification and increased polypeptide levels" and quotes Pennica *et al.*, Haynes *et al.*, and Hu *et al.* for support. The Examiner maintains that "given the small increase in gene amplification of PRO1182 and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a small increase or decrease in gene amplification would correlate with experimentally significant increased or decreased **mRNA or polypeptide levels**" (Emphasis added).

For the reasons outlined below, Applicants respectfully disagree and traverse this rejection with respect to Claims 124, 129-131, 135-150. Applicants submit that not only has the Patent Office not established a *prima facie* case for lack of utility and enablement, but that the PRO1182 gene possesses a credible, specific and substantial asserted utility and is fully enabled.

### A. The Results of the Gene Amplification Assay Provide Utility for Claims 124, 129-131 and 135-145

First of all, Applicants maintain the position that the specification discloses at least one credible, substantial and specific asserted utility for the PRO1182 gene for the reasons previously

set forth in Applicants' Responses filed on June 24, 2004, December 20, 2004 and June 23, 2005. As discussed in Applicants' Response of June 23, 2005, Applicants rely, in part, on the gene amplification data for patentable utility of the PRO1182 gene (for Claims 124, 129-131 and 135-145), which is clearly disclosed in the instant specification under Example 170. Applicants submit that the Examiner seems to be applying a heightened utility standard in this instance, which is legally incorrect. Whether the "increase" in gene amplification is "significant" is what needs to be addressed. The specification discloses that the nucleic acids encoding PRO1182 had $\Delta$Ct value of > 1.0, which is a **more than 2-fold increase**. As explained in the passage on page 539, lines 37-39, "the results of TaqMan™ PCR are reported in $\Delta$Ct units. **One unit** corresponds to one PCR cycle or approximately a **2-fold amplification**, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on" (emphasis added). Table 9C says that PRO1182 showed approximately 1.43-1.81 $\Delta$Ct units which corresponds to $2^{1.43}$ -$2^{1.81}$- fold amplification or **2.6945 fold to 3.506-fold** amplification in lung adenocarcinomas. Accordingly, the present specification clearly discloses strong evidence that the PRO1182 gene is significantly amplified in a significant number of lung adenocarcinoma tumors.

As evidence that the "increase in DNA" in the gene amplification assay is significant, Applicants submitted a Declaration by Dr. Audrey Goddard in their Response filed December 20, 2004. Applicants particularly draw the Examiner's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

As indicated above, the gene encoding the PRO1182 polypeptide shows at least a two fold amplification in several lung tumor cell lines. In addition, the Goddard Declaration clearly establishes that the TaqMan real-time PCR method described in Example 170 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that the PRO1182 gene is a diagnostic marker for lung adenocarcinoma.

**B. The Utility of the Claimed Nucleic Acids Does Not Depend Upon the Properties of the Encoded Polypeptide**

Applicants respectfully draw the Examiner's attention to the fact that, the instant claims are directed to nucleic acids, not polypeptides, therefore, the issue of whether there is a correlation between gene amplification and polypeptide expression levels is irrelevant. One of skill in the art would understand how to use the claimed nucleic acids to detect amplification of the gene encoding PRO1182, and how to use the gene amplification results to diagnose cancer. Thus, the question of whether or not PRO1182 mRNA or polypeptide levels are also increased in these cancers has no relevance to the utility of the claimed nucleic acid molecules.

The claimed nucleic acids can be used in cancer diagnosis without any knowledge regarding the function or cellular role of the encoded protein. Applicants submit that the law clearly states that "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *Newman v. Quigg*, 11 USPQ2d 1340 (Fed. Cir. 1989). Accordingly, the disclosure or identification of the mechanism by which PRO1182 is associated with cancer is not required in order to establish the patentable utility of the claimed PRO1182 nucleic acids.

**C. A *prima facie* Case of Lack of Utility Has Not Been Established**

The Examiner cites Pennica *et al.* and Haynes *et al.* to show that "there is a lack of correlation between DNA amplification and mRNA levels" and further quotes Hu *et al.* to show that " the literature cautions researchers against drawing conclusions based on small changes in

transcript expression levels between normal and cancerous tissues." Applicants strongly disagree.

As discussed above, the increase in DNA copy number for the PRO1182 gene is significant and would not be considered "small" according to the Goddard Declaration. Moreover, as also discussed above, the question of whether or not PRO1182 mRNA or polypeptide levels are also increased in these cancers has no relevance to the utility of the claimed nucleic acid molecules. Even assuming arguendo, if the cited references were relevant to the present invention, Applicants maintain that their teachings do not support a *prima facie* case of lack of utility.

The legal standard for utility has been discussed in detail in the previous responses. Applicants respectfully remind the Examiner that the evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[1] Thus, to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Applicant.

Pennica *et al.* does not address genes in general and bases its conclusion only on one gene family, the WISP gene family. And the Haynes *et al.* reference in fact supports the Applicants' position that in general, polypeptide levels increase when mRNA levels increase (see Haynes Figure 1). Furthermore, contrary to the Examiner's assertion, the Hu *et al.* reference also does not conclusively establish a *prima facie* case for lack of utility for the PRO1182 molecule. The Hu *et al.* reference is entitled "Analysis of Genomic and Proteomic Data using Advanced Literature Mining" (Emphasis added). Therefore, as the title itself suggests, the conclusions in this reference are based upon statistical analysis of information obtained from published literature, and not from experimental data. Hu *et al.* performed statistical analysis to provide evidence for a relationship between mRNA expression and biological function of a given molecule (as in disease). The conclusions of Hu *et al.* however, only apply to a specific type of

breast tumor (estrogen receptor (ER)-positive breast tumor) and cannot be generalized to breast cancer genes in general, let alone to cancer genes in general. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column). In other words, some molecules studied in Hu may have been underrepresented merely because they were less frequently cited or studied in literature compared to other more well-cited or studied genes. Therefore, Hu *et al.*'s conclusions are not based on genes/mRNA *in general* and therefore, the conclusions drawn by the Examiner based upon Hu are not reliably supported.

In conclusion, when the proper legal standard is used, a *prima facie* case of lack of utility has not been met based on the cited references Pennica *et al.*, Haynes *et al.* or Hu *et al.* by the Examiner. On the other hand, based on the application of proper legal standards, the appropriate conclusion is that the present application does in fact disclose at least one patentable utility for the PRO1182 gene of Claims 124, 129-131 and 135-145 based on the gene amplification utility.

Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1182 gene, that the claimed PRO1182 gene is useful, for example, in the diagnosis of lung cancer, and would have known exactly how to use the claimed genes without any undue experimentation.

### D. The Results of the Adipocyte Glucose/FFA Uptake Assay Provide Utility for the Nucleic Acids Encoding PRO1182 Polypeptides of Claims 124, 129-131, 135-138 and 146-150

The Examiner further rejects any utility based on 'the adipocyte glucose/FFA uptake assay,' (Example 149) and says that "each of the references cited by the Applicants teaches that the agents utilized in the assays *enhance* glucose uptake by adipocyte cells, not inhibit glucose uptake..." (see page 7, lines 13-14 of Office Action; emphasis added). On page 8, last two lines of the Office Action, the Examiner states that "the proposed use of the claimed PRO1182 polypeptides is simply a starting point for further research and investigation into potential practical uses of the polypeptides." Applicants respectfully disagree. The Examiner's is also concerned that "the instant specification does not report any specific or statistical differences," or

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[1] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

in other words, the Examiner is concerned with the *efficacy* with which the PRO1182 polypeptides enhances glucose uptake. Applicants submit that these concerns are misplaced and is not proper basis for a utility rejection of the present claims.

**E. PRO1182 is a *Simulator* of Glucose and/or FFA Uptake**

Applicants submit that due to an error, the PRO1182 molecule was inadvertently indicated as an inhibitor of glucose uptake in the previous response filed on June 23, 2005. On the other hand, as clearly indicated in the instant specification, at least in Example 158, page 530, lines 13-15, PRO1182 is a ***stimulator*** of glucose and/or FFA uptake in the assay and therefore enhances glucose uptake by adipocyte cells. Hence, any rejections directed to the PRO1182 molecule as not enhancing glucose uptake are rendered moot.

As discussed in Applicants' Response filed June 23, 2005, it was known in the art at the time of filing that agents which increased glucose uptake, such as troglitazone and pioglitazone, were useful in the treatment of diabetes. Treatment with vanadium salts, another agent which increased glucose uptake, was shown to lower glucose levels in hyperglycemic rats. Diabetes, hyperglycemia, and obesity were know at the time of filing to be closely linked conditions (see, for example, Sandouk, page 352). Thus, one of skill in the art would have understood that stimulators of glucose uptake would be useful in the treatment of diabetes, obesity, and hyperglycemia. Accordingly, a variety of real-life utilities, such as treatments for glucose uptake related diseases, including obesity and diabetes, are envisioned for PRO1182 based on the glucose/FFA uptake assay results disclosed herein. Therefore, nucleic acids encoding PRO1182 also have utility and would be therapeutically effective in treating disorders including, but not limited to, include obesity, diabetes, and hyper- or hypo-insulinemia.

**F. The Precise Mechanism Need Not be Understood for Attaining the Asserted Utility**

Applicants respectfully submit that, the fact remains that the results of the adipocyte glucose/FFA uptake assay was positive for the PRO1182 polypeptide, and are useful in *enhancing* glucose uptake by adipocyte cells, as discussed above. The Examiner's concern that the results were an invitation to experiment further, whether correct or incorrect, do not negate the positive results of the assay, and further, do not negate the action of the PRO1182

polypeptides or Applicants' assertion of utility. As the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."[2] A considerable amount of experimentation is permissible, if it is merely routine. Thus, one skilled in the art would know how to make and test the polypeptides encoded by the claimed nucleic acids in the glucose/FFA uptake assay.

Regarding the Examiner's concern regarding the *efficacy* of the PRO1182 polypeptides to enhance glucose uptake, Applicants submit that, it appears that the Examiner's concern is with regard to the underlying mechanism due to which the positive results of the adipocyte glucose/FFA uptake assay occur, and not with the results themselves. However, as stated by the Federal Circuit, "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortwright*, 165 F.2d 1353, 1359 (Fed. Cir. 1999). Thus, the precise mechanism for the asserted utility need not be understood for attaining the asserted utility.

The Examiner adds regarding the supportive references cited by the Applicants in the previous response that "Tafuri *et al.*, Sandouk *et al.*, Goldwaser *et al.*, Mueller *et al.* (1998) and Mueller *et al.* (2000) *teach different methodologies* for the measurement of glucose uptake in adipocyte cells as compared to the glucose assay of the instant specification....None of the references utilizes the stimulatory and inhibitory scale disclosed in the instant specification...the instant specification does not report any specific or statistical differences and there is no indication in the specification as to how PRO1182 inhibited glucose uptake as compared to control or whether the results were significant." (Emphasis added; see first paragraph of page 9 of the Office Action).

Applicants submit that such a rejection again lacks a proper basis for a utility rejection. The present glucose/FFA assay/method need not be the same or superior to other methods for attaining the asserted utility. The Federal Circuit has stated that "[a]n invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in

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[2] M.P.E.P. §2164.01 citing *In re Certain Limited-charge Cell Culture Microcarriers,* 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), *aff' sub nom. Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985).

certain applications: "[T]he fact that an invention has only limited utility and is not operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.* 730 F.2d 753,762, 221 U.S.P.Q. 473,480 (Fed. Cir. 1984)." *Stiftung v. Renishaw PLC* 945 F.2d 1173, 1180 (Fed. Cir. 1991). In fact, the Examiner herself acknowledges that "similar assays are commonly used **to identify potential anti-diabetic agents** and to examine the regulatory mechanisms of important molecules involved in fat cell metabolism" (emphasis added; see page 8, lines 4-7 of the Office Action). Therefore, PRO1182 polypeptides and their antibodies would be therapeutically useful in treating disorders including, but not limited to, include obesity, diabetes, and hyper- or hypo-insulinemia. One of ordinary skill in the art, in possession of these results, would, more likely than not, believe that the PRO1182 polypeptides are useful for their asserted utility and would also know that the PRO1182 nucleic acid sequences are therefore useful. Accordingly, Applicants respectfully submit that Applicants' assertion that the claimed nucleic acids encoding PRO1182 proteins have utility in the field of treatment of metabolic diseases such as diabetes, obesity, etc. is substantial.[3]

In view of the above, Applicants respectfully submit that the specification discloses at least one credible, substantial and specific asserted utility for the nucleic acids encoding the polypeptide PRO1182 of Claims 124, 129-131, 135-138 and 146-150. Further, based on this utility, the disclosure in the specification, the well-established knowledge in the art (at the effective date of filing) regarding agents that modulate or regulate glucose uptake and their usefulness in treatment of metabolic diseases, one skilled in the art would have known how to make and use the claimed nucleic acids of Claims 124, 129-131, 135-138 and 146-150.

Accordingly, the Examiner is requested to reconsider and withdraw the present rejection under 35 U.S.C. §101 and §112, first paragraph.

**Claim Rejections - 35 U.S.C. §112, First Paragraph - Written Description**

Claims 124, 129-131, 135-150 are rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description. In particular, the Examiner maintains that Applicants have not "described or shown possession of all polynucleotides 80-99% homology to SEQ ID NO:356,

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[3] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

that still retain the function of SEQ ID NO:356." Applicants respectfully traverse this rejection to the pending claims.

**The Specification Provides Sufficient Written Description for the Claimed Invention:**

The legal standards for evaluating Written Description was discussed in the previous response. Whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

Applicants respectfully submit that the instant invention evidences the actual reduction to practice of full-length PRO1182 of SEQ ID NO: 357, the nucleic acid encoding PRO1182 (SEQ ID NO: 356) and the nucleic acid deposited under ATCC accession number 203088 that encodes PRO1182. Further the amended claims recite the functional recitation: "the polypeptide encoded by said nucleic acid inhibits the uptake of glucose or FFA (free fatty acids) by adipocyte cells" which, as discussed above, is based on a well-established assay known to the skilled artisan at the effective filing date of this application. Therefore, the claimed nucleic acids are defined both by functional as well as structural features.

The Examiner's attention is respectfully directed to Example 14 of the Synopsis of Application of Written Description Guidelines issued by the U.S. Patent Office, which clearly states that protein variants meet the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if: (1) the procedures for making such variant proteins are routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein, and (3) the variant proteins possess the specified functional activity and at least 95% sequence identity to the reference sequence. Thus, this particular combination of functional activity and structural homology, as disclosed in the specification, has been recognized by the USPTO as sufficient to describe a claimed genus of polypeptides. More recently, in *Enzo Biochem., Inc. v. Genprobe, Inc.* 296 F.3d 1316 (Fed. Cir. 2002), the court adopted the standard

that "the written description requirement can be met by 'showing that the invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, . . . *i.e.,* complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Id.* at 1324. Indeed, the court adopted the standard from the USPTO's Written Description Examination Guidelines, which apply to both proteins and nucleic acids. Current applicable case law holds that biological sequences are not adequately described **solely** by a description of their desired functional activities.

The instant claims meet the standard set by the *Enzo* court in that the claimed sequences are defined not only by functional properties, but also by structural limitations. It is well established that a **combination** of functional and structural features may suffice to describe a claimed genus. "An Applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that Applicant was in possession of the claimed invention, *i.e.,* complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."[4] The recited property of enhancing glucose uptake by PRO1182 adds to the characterization of the claimed nucleic acids sequences which encode PRO1182 in a manner that one of skill in the art could readily assess and understand.

Thus, the genus of nucleic acids with at least 80-99% sequence identity to SEQ ID NO:356, which possess the functional property of enhancing glucose or FFA (free fatty acids) uptake by adipocyte cells, and would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description. Accordingly, one skilled in the art would have known that Applicants had knowledge and possessed the claimed nucleic acids with 80-99% sequence identity to SEQ ID NO: 356.

Further, the instant specification provides methods for determining percent identity between two nucleic acid sequences and teaches specific parameters to be associated with the

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[4] M.P.E.P. §2163 II(A)(3)(a)

term "percent identity" as applied to the present invention. From the specific activity of the claimed nucleic acids encoding the PRO1182 polypeptide, the description of the claimed genus is achieved.

Hence, Applicants respectfully request that this rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C64**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

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